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The Role of Inflammation in Subventricular Zone Cancer

Chiara Bardella[4#], Abeer R. Al-Shammari[2#], Luana Soares[1,3#], Ian Tomlinson[4], Eric O'Neill[3] and Francis G. Szele[1*]

[1]Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford UK.
[2]Research and Development, Qatar Research Leadership Program, Qatar Foundation, Doha, Qatar.
[3]Department of Oncology, University of Oxford, Oxford UK.
[4]Institute of Cancer and Genomics Sciences, University of Birmingham, Birmingham UK.
[#] Equal contributions

*Corresponding author:
Francis G. Szele, PhD
Department of Physiology, Anatomy, and Genetics
University of Oxford
South Parks Road
Oxford, UK
OX1 3QX
Francis.Szele@dpag.ox.ac.uk

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This review is dedicated to the loving memory of Francis Harangozo and Cornelia Szele.

Abstract (250/250 max)

The adult subventricular zone (SVZ) stem cell niche has proven vital for discovering neurodevelopmental mechanisms and holds great potential in medicine for neurodegenerative diseases. Yet the SVZ holds a dark side - it can become tumorigenic. Glioblastomas can arise from the SVZ via cancer stem cells (CSCs). Glioblastoma and other brain cancers often have dismal prognoses since they are resistant to treatment. In this review we argue that the SVZ is susceptible to cancer because it contains stem cells, migratory progenitors and unusual inflammation. Theoretically, SVZ stem cells can convert to CSCs more readily than can postmitotic neural cells. Additionally, the robust long-distance migration of SVZ progenitors can be subverted upon tumorigenesis to an infiltrative phenotype. There is evidence that the SVZ, even in health, exhibits chronic low-grade cellular and molecular inflammation. Its inflammatory response to brain injuries and disease differs from that of other brain regions. We hypothesize that the SVZ inflammatory environment can predispose cells to novel mutations and exacerbate cancer phenotypes. This can be studied in animal models in which human mutations related to cancer are knocked into the SVZ to induce tumorigenesis and the CSC immune interactions that precede full-blown cancer. Importantly inflammation can be pharmacologically modulated providing an avenue to brain cancer management and treatment. The SVZ is accessible by virtue of its location surrounding the lateral ventricles and CSCs in the SVZ can be targeted with a variety of pharmacotherapies. Thus, the SVZ can yield aggressive tumors but can be targeted via several strategies.

Abbreviations
ASPP2, apoptosis-stimulating protein of p53 with signature sequences of ankyrin repeat-, SH3 domain-, and proline-rich region-containing protein 2; **CD**, complement of differentiation; **CNS**, central nervous system; **CP**, choroid plexus; **CSC**, cancer stem cell; **CSF,** cerebrospinal fluid; **EGF**, epidermal growth factor; **EGFr**, epidermal growth factor receptor; **EPO**, erythropoeitin; **FGF2**, Fibroblast growth factor 2; **GBM,** glioblastoma multiforme, **GFAP**, glial fibrillary acidic protein; **G-CSF**, granulocyte colony-stimulating factor; **HGF,** hepatocyte growth factor; **IDH1**, isocitrate dehydrogeniase 1; **IFN-γ**, gamma interferon; **IGF-1**, insulin growth factor-1; **IL-10**, interleukin 10; **iPSC**, induced pluripotent stem cell; **NSC**, neural stem cell; **OCT4,** octamer-binding transcription factor 4; **PDGF**, platelet-derived growth factor; **PDGFr**, platelet-derived growth factor receptor; **RCAS**, replication competent avian-like sarcoma; **RMS**, rostral migratory stream; **ROS**, reactive oxygen species; **SCNT**, somatic cell nuclear transfer; **SDF-1**, stromal cell derived factor-1; **SHH**, sonic hedgehog; **SVZ,** subventricular zone; **TAP**, transit amplifying progenitor; **TMEV**, Thelier's murine encephalomyelitis virus; **TNFα**, tumor necrosis factor-alpha; **VEGF**, vascular endothelial growth factor.

Key Words: subventricular zone, cancer stem cells, inflammation

Contents

1. Introduction

The past two decades have witnessed an explosion of information demonstrating that endogenous tissue stem cell niches can harbour cancer stem cells. Many of the molecular regulatory pathways driving normal development and maintaining tissue homeostasis can be subverted in cancer (Canoll and Goldman, 2008). The mammalian brain contains three neural stem cell (NSC) niches that continuously produce new neurons throughout life; the subventricular zone (SVZ) lining the lateral ventricle, the subgranular zone (SGZ) of the hippocampal dentate gyrus and the mediobasal hypothalamus (Alvarez-Buylla and Lim, 2004; Recabal *et al.*, 2017). Hypothalamic neurogenesis is the most recently discovered niche, is the most poorly understood and has not been confirmed in humans. Neuroblasts generated in the SGZ move a short distance to the granular cell layer where they differentiate into dentate gyrus granule neurons that are thought to influence memory (Cameron *et al.*, 1993; Lacar *et al.*, 2014). Hippocampal and hypothalamic cancers are rare and less is known about inflammation in these niches than in the SVZ. Therefore, in this review we will concentrate on the SVZ and mostly ignore the hippocampal and hypothalamic niches.

The adult SVZ generates the largest number of cells of the three niches, mostly producing neuroblasts (Fig. 1D). The newborn cells travel long distances from the SVZ via the rostral migratory stream (RMS) into the olfactory bulbs (OB) where they differentiate into periglomerular or granule local interneurons (Doetsch and Alvarez-Buylla, 1996). The SVZ lines the lateral ventricles and multiciliated ependymal cells separate the SVZ from the circulating cerebrospinal fluid (CSF). The SVZ niche contains multiple cell types (type B, C and A cells), which also include microglia, the primary immune cells of the brain (Doetsch *et al.*, 1997; Dulken *et al.*, 2017). Type B cells have astrocytic characteristics and are subdivided into type B1 and B2 cells. B1 cells have direct contact with the lateral ventricle (LV) and act as self-renewing neural stem cells whereas B2 cells do not maintain direct contact with the LV and act as niche astrocytes. Type B1 cells give rise to transit amplifying progenitors (TAP) (C cells) that actively divide and generate immature neuroblasts (A cells) that migrate to the OB (Doetsch *et al.*, 1999; Garcia *et al.*, 2004; Ihrie and Alvarez-Buylla, 2011). In addition to neurons, the postnatal SVZ generates progenitors that migrate from the SVZ throughout the forebrain and differentiate into astrocytes and oligodendrocytes (Levison and Goldman, 1993). A central theme of our review is that this developmental event is recapitulated and dysfunctional in SVZ cancers.

The human SVZ is somewhat different compared to its rodent counterparts. In infants the human SVZ generates neuroblasts that migrate not only to the olfactory bulb but also into the cerebral cortex (Paredes *et al.*, 2016; Sanai *et al.*, 2011). In the adult human there is little evidence for migration of neuroblasts from the SVZ to the OB (Sanai *et al.*, 2004). However the adult human SVZ is thought to generate progenitors that migrate laterally to the caudate nucleus and differentiate into interneurons (Ernst *et al.*, 2014). The discovery of adult human neurogenesis has injected great hope into the idea that stimulating these stem cells for endogenous repair of brain injuries or neurodegenerative diseases could be a viable therapeutic intervention (Young *et al.*, 2011a). It is well documented that stem cells and progenitors increase proliferation in response to animal models of neurological disease as well as in human patients and that cells born in the SVZ migrate actively towards the injuries (Chang *et al.*, 2016; Dizon and Szele, 2005; Szele and Chesselet, 1996). The cells generated by the neurogenic niches can be neuroprotective via generation of growth factors and dampening of inflammation (Pluchino *et al.*, 2009; Pluchino *et al.*, 2005).

Nevertheless, Murphy's law seems to exist in biology and "when something can go wrong it will". The most dramatic example of this in the SVZ is that instead of contributing to regeneration, the niche generates and/or supports cancer. The cancer stem cell (CSC) hypothesis suggests that a tumor is maintained over time by a small subset of cancer cells with stem cell-like properties, i.e. unlimited self-renewal, multipotency and tumor initiating capacity. Although controversial, the existence of a subpopulation of cancer cells endowed with these properties has been described in some non-solid and solid tumors, including brain cancer (Beier *et al.*, 2007; Chen *et al.*, 2010; Clarke *et al.*, 2000; Galli *et al.*, 2004; Mazzoleni *et al.*, 2010; Singh *et al.*, 2004). Consequently, adult SVZ NSCs and progenitors have been suggested as a source for CSCs. The SVZ niche is thought to be a tumor reservoir for a range of high grade gliomas, including adult glioblastoma, the most common and most malignant glioma (Fig. 2). Resistance of glioblastoma to therapy and its rapid recurrence are believed to be caused by CSCs in the tumor. Notably, gliomas in close contact with the SVZ are more aggressive compared to ones distant from this site (Adeberg *et al.*, 2014a; Chaichana *et al.*, 2008; Gollapalli *et al.*, 2017; Jafri *et al.*, 2013; Mistry *et al.*, 2017a; Mistry *et al.*, 2017b; Young *et al.*, 2011b). These tumors show increased recurrence and resistance to therapy, further suggesting they arise from and are maintained by CSCs (Chen *et al.*, 2015; Sonoda *et al.*, 2014). The evidence for SVZ-associated tumors arising from CSCs is still rather indirect, but as described in later sections of our review this possibility is testable.

Most tumors are associated with inflammation, and despite its heterogeneity, inflammation is a cancer risk factor in general which can exacerbate malignancy. It is well-established that the SVZ niche is bathed in a unique soup of chemokines, cytokines and growth factors. In this review we will explore less well-known evidence that regulation of inflammation in the SVZ is unusual and that this can contribute to SVZ tumorigenesis. Although the brain has long been considered to be "immune-privileged", this concept is now less accepted (Engelhardt *et al.*, 2017), and in fact, the SVZ and adjacent choroid plexus seem to be a hot-spot of inflammation and immune activity. Secreted molecules produced by different SVZ cells result in complex regulation of proliferation, differentiation and survival. Interestingly, many of the molecules produced by the SVZ niche are identical to those released by inflammatory cells which drive tumorigenesis. These include the epidermal growth factor (EGF) and the angiogenic growth factors vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2) in addition to chemokines and cytokines that amplify the inflammatory state. In uncontrolled conditions the signaling molecules produced in the SVZ could generate a response resembling that present in chronic inflammatory tissue. Hence an intriguing hypothesis is that the “inflammatory” signals released in the SVZ may be important in creating and maintaining CSCs. We finish the review by suggesting that the location of the SVZ predisposes it to be a target for cancer therapeutic interventions.

2. The Inflammatory Subventricular Zone

Microglia and inflammation regulate various aspects of brain development via direct sculpting of cells and synapses and by altering the cytokine milieu. Microglia phagocytize neural progenitor cells during cerebral cortex development in rodents and primates and can be modulated by anti-inflammatory agents (Cunningham *et al.*, 2013). Microglia are also known to consume neural progenitor cells in the hippocampal SGZ and thereby

regulate their numbers (Sierra *et al.*, 2010). Could microglia also be targeted for clearance of CSCs or other downstream transformed cells? Neither this question nor whether microglia phagocytize SVZ cells in health or disease is well understood. What is known however is that SVZ inflammation is constitutively semi-activated, that it is unusually regulated, and that the SVZ lines the CSF-brain barrier, potentially exposing it to pathogens. We will describe these features and also data showing that the choroid plexus harbours immune cells poised for activation and that it influences the molecular composition of the CSF.

Microglia also sculpt circuits during neural development via synaptic phagocytosis which helps eliminate unused circuits (Schafer *et al.*, 2012). An interesting aspect of SVZ anatomy is that many axon terminals abut the niche without entering it whereas others directly enter the niche. Dopaminergic nigrostriatal axon terminals seem to have a barrier at the SVZ-striatal interface (Ramaswamy *et al.*, 2005). Nevertheless dopamine released by nigrostriatal neurons diffuses into the SVZ and binds to dopamine receptors, thereby regulating neurogenesis (Hoglinger *et al.*, 2004; Kim *et al.*, 2010). In contrast, there is evidence that axon terminals of striatal GABAergic, septal cholinergic and serotonergic neurons are all found amongst SVZ cells (Banasr *et al.*, 2004; Paez-Gonzalez *et al.*, 2014; Young *et al.*, 2014b). The neurotransmitters released by these neurons regulate SVZ proliferation and other functions (Banasr *et al.*, 2004; Paez-Gonzalez *et al.*, 2014; Young *et al.*, 2014b). Recently, pro-opiomelanocortin (POMC) hypothalamic neurons were shown to project axon terminals specifically into the anterior ventral SVZ and thereby regulate hunger-mediated neurogenesis (Paul *et al.*, 2017). Thus it may be that during development as in homeostasis, SVZ microglia phagocytize axonal inputs to limit their density or control their location in the SVZ. We predict that this process occurs and that it may be dysregulated in cancer, changing the balance of neurotransmitters, SVZ proliferative homeostasis and ultimately contributing to disease progression.

2.1. The SVZ is a unique inflammatory niche at the cellular level

Several lines of research over the past decade indicate that in contrast to the rest of the brain, the SVZ is constitutively semi-inflamed (Goings *et al.*, 2006). Inflammation is quite differently regulated during embryogenesis and early life, and given that the SVZ is neurodevelopmentally active throughout life, this is not completely surprising. Two to five percent of SVZ cells are microglia and they are evenly distributed amongst the other SVZ cells. Electron microscopy shows that their processes make extensive contacts with all cell types in the niche and also with ependymal and RMS cells (Goings *et al.*, 2006; Yang *et al.*, 2004). In healthy mice, SVZ microglial expression of CD45 and other microglial markers such as isolectin B4 is higher than in other brain regions (Goings *et al.*, 2006). SVZ microglia also proliferate at higher rates (~5 fold or more) compared to corpus callosum or striatal microglia, respectively (Goings *et al.*, 2006). In contrast to the SVZ, hippocampal SGZ microglia are not semi-inflamed in homeostasis (Goings *et al.*, 2006) whereas there is some evidence suggesting the hypothalamic NSC niche exhibits constitutive inflammation (Zhang *et al.*, 2013).

More recent studies have also found that microglia in the SVZ exhibit different characteristics from microglia found in the adjacent parenchyma. Young postnatal rat SVZ microglia expressed high levels of CD68 and had amoeboid morphology, both indicators of activation (Shigemoto-Mogami *et al.*, 2014). Adult mouse microglia in the SVZ express lower levels of purinergic receptors compared to other microglia and are unable to respond

to ATP with chemotaxis (Ribeiro Xavier *et al.*, 2015a). As was observed in earlier work (Goings *et al.*, 2006), murine SVZ microglia appeared to be in a morphological state of semi-activation with enlarged cell bodies and processes that were shorter and thicker than striatal or cortical microglia (Ribeiro Xavier *et al.*, 2015a). Recently it was shown that the anti-inflammatory drug minocycline increases SVZ neurosphere proliferation and stem cell numbers, possibly in a microglia-independent manner suggesting that anti-inflammatory agents may directly modulate the SVZ niche (Kuroda *et al.*, 2017). A major remaining question however, is whether the human SVZ also harbours activated or semi-activated microglia and if it is also constitutively semi-inflamed. If so, then this may contribute to the generation and evolution of SVZ-derived cancer.

Complementing the microglial differences in homeostasis, multiple experiments show that SVZ inflammation in response to injury is difficult to predict and differs from surrounding inflammation. Cerebral cortex injury robustly activated microglia in the corpus callosum and in the striatum but remarkably, not in the immediately adjacent SVZ, even in regions of the niche that were close to the injury (Goings *et al.*, 2006). This study was the first to point out that inflammation is unusually regulated in the SVZ and that the cellular response therein is dramatically different from adjacent regions of the brain. Although microglia were resistant to activation after cortical injury, SVZ astrocytes exhibited increased glial fibrillary acidic protein (GFAP) expression which is indicative of astrocytic inflammation (Sundholm-Peters *et al.*, 2005), suggesting that though microglial inflammation is unique in the SVZ, astrocytic inflammation may be regulated similarly to the parenchyma. In line with this notion, the middle cerebral artery occlusion (MCAO) model of cortical and striatal stroke caused marked astrocytic reactivity in these regions as well as in the SVZ, however it did not change the percentage of mitotic microglial cells in the SVZ, which was only one hundred microns or so from the edge of the lesion (Young *et al.*, 2013). Inflammation is often associated with apoptosis and indeed MCAO caused robust apoptosis in the striatum but not in the SVZ (Young *et al.*, 2013). We do not know if cell death in glioblastoma or other SVZ-related cancers is differentially regulated in the niche compared to the rest of the brain. However apoptosis is an important event in regulating cancer, making this question important for future in-depth study.

Several other studies confirm the SVZ has unpredictable inflammatory responses to disease, with the example of multiple sclerosis models being the most pertinent (Goings *et al.*, 2008; Hillis *et al.*, 2016; James *et al.*, 2016). In contrast to the cortical and stroke-like lesions just mentioned, a viral model of chronic progressive demyelination (Thelier's murine encephalomyelitis virus, TMEV) targeted the SVZ with early, predictable, consistent and massive inflammation even though inflammation was stochastic in the rest of the CNS (Goings *et al.*, 2008; James *et al.*, 2016). Whereas the large majority of CD45+ immune cells in the SVZ are microglia, TMEV induced massive infiltration of T cells into the niche (James *et al.*, 2016). In sharp contrast to TMEV, mild reversible demyelination achieved by cuprizone toxicity caused inflammation in the corpus callosum and striatum but not in the immediately adjacent SVZ. There was no evidence that inflammation had increased compared to healthy controls, and in fact the number of CD45+ cells was decreased after cuprizone (Hillis *et al.*, 2016). As well, the number of mitotic cells, which is associated with gliosis in brain inflammation increased in the corpus callosum and striatum immediately adjacent to the SVZ, but decreased in the stem cell niche after cuprizone demyelination (Hillis *et al.*, 2016).

Much work has been carried out in the last two decades to understand the SVZ response to injury and disease in the hope of optimizing the endogenous neuro-

regenerative capacity of the niche (Chang *et al.*, 2016; Dizon and Szele, 2005; Kim and Szele, 2008; Young *et al.*, 2011a). Yet only a minority of these studies has considered how the regulation of inflammation impacts the SVZ's response to pathology. In light of findings emphasizing the importance of inflammation in the SVZ further studies will have to pay closer attention to this in the context of injury. Cancer usually induces inflammation but the data above suggest that different types of cancer may increase, have no effect or even decrease SVZ inflammation. It will be important for new studies to discern the range of inflammatory responses in the SVZ to different types of cancer.

2.2. Immune cells enter the brain through the SVZ

Microglia are the resident macrophages in the brain and are involved in active immune responses against infection and injury. In rodents, macrophages that are generated in the yolk sac at embryonic day 8 (E8) start to colonize the neuroepithelium from E9/E9.5 and give rise to embryonic microglia (Ginhoux *et al.*, 2013). The blood-brain barrier (BBB) starts to appear at E13.5 isolating the CNS from peripheral macrophages. However, older data suggested that the SVZ is a major route of entry into the brain of immune cells during normal perinatal periods of development (Mohri *et al.*, 2003). Resident microglia in the brain parenchyma expand through local proliferation during late embryonic to early postnatal development. In adulthood, bone marrow (BM) derived macrophages may cross the BBB during inflammation in order to supplement local microglial populations in the brain (Ginhoux *et al.*, 2013). After cortical injury, peripheral macrophages labelled with fluorescent microbeads entered the brain and SVZ in a few hours and then equally rapidly exited (Goings *et al.*, 2006). The same lesions induced SVZ microglia to migrate towards the cortex (Goings *et al.*, 2006). Systemic inflammation may trigger migration of leukocytes from the bloodstream into the CNS where they differentiate into resident macrophages or dendritic cells. The likelihood of leukocyte infiltration into the brain may rely on the blood-brain barrier, which is developmentally regulated, with a gradual increase in permeability with age. The blood-brain barrier collectively describes four main interfaces between the CNS and the periphery: blood-brain barrier, blood-CSF barrier, outer CSF-brain barrier and inner CSF-brain barrier. The blood-CSF barrier at the choroid plexus (CP) has higher permeability than the other barriers (Stolp *et al.*, 2005), and the SVZ is located adjacent to the choroid plexus. Interestingly, CD45+ immune cells can be observed with processes that span the choroid plexus and the SVZ (Goings *et al.*, 2006). Therefore, infiltration of systemic molecules or cells is likely to be highly specialized in the SVZ region.

2.2.1. The choroid plexus flanks and influences the SVZ

The CP, a thin epithelial tissue located in the ventricular system, has a high secretory capacity and produces the majority of the CSF in the vertebrate brain. The choroid plexus is mainly composed of a single layer of epithelial cells surrounding a stromal core of fenestrated blood vessels, fibroblasts and immune cells such as macrophages and dendritic cells. The tight junctions between adjacent epithelial cells prevent paracellular passage of blood cells into the CSF (Falcao *et al.*, 2012). As such the choroid plexus comprises the blood-CSF barrier. However, the epithelial cells express several transporters that allow the passage of water, ions and small molecules including nutrients and vitamins. In addition, CP epithelial cells express receptors for various molecules including neurotransmitters, cytokines and toxins that affect downstream signaling pathways and proteins secreted from the choroid plexus (Falcao *et al.*, 2012). The CP also harbours specialized T cells that respond to brain antigens as well as signals

from the circulation suggesting it may be a good target for immune modulation (Baruch and Schwartz, 2013; Schwartz and Baruch, 2014). Despite these insightful observations, very little is known about CP immune activation during SVZ oncogenesis and how the specialized T cells in the CP may influence SVZ tumorigenesis.

SVZ neural stem cells or type B1 cells are located immediately beneath the ependymal layer that surrounds the lateral ventricles. Type B1 cells maintain direct contact with the circulating CSF through a short non-motile apical cilium that extends towards and has direct contact with the lateral ventricles. Of interest, the choroid plexus releases various factors into the CSF that support the recruitment and proliferation of SVZ neural stem cells and their progeny (Silva-Vargas *et al.*, 2016). This is conceptually similar to the effects of embryonic CSF on brain development (Lehtinen *et al.*, 2013; Lehtinen and Walsh, 2011). The choroid plexus secretome normally changes throughout life which especially affects SVZ neural stem cells under basal conditions (Silva-Vargas *et al.*, 2016). During peripheral inflammation, choroid plexus secretion is changed in ways that ultimately affect CSF composition (Marques *et al.*, 2008; Marques *et al.*, 2009). Although previous studies demonstrated the impact of neuroinflammation in the SVZ stem cell niche (Liu *et al.*, 2013; Pluchino *et al.*, 2008), it remains unclear whether inflammation-induced molecular changes in the choroid plexus *per se* directly affect SVZ cells during postnatal development. In particular, it would be interesting for future studies to determine whether disrupted secretion from the choroid plexus *per se* is directly involved in the progression of pathological conditions such as brain cancer.

2.3. SVZ inflammation at the molecular level

Several lines of evidence suggest that inflammation regulating-molecules are expressed in the SVZ. A few groups have used RNAseq to determine levels of heterogeneity in the SVZ lineage and have elucidated transcriptional regulation of these states. Overall they have shown that there are several more states of stem cell quiescence versus activation than previously appreciated, but they have also contributed insights into how SVZ inflammation regulates this transition. Single cell RNAseq demonstrated that after brain ischemia, gamma interferon (IFN-γ) induces dormant stem cells to enter an activated state (Llorens-Bobadilla *et al.*, 2015). Another recent single-cell RNAseq study indicated that SVZ cells cultured as neurospheres expressed higher levels of genes associated with inflammation such as Fas and Ifitm3, and cytokine signaling than did in vivo SVZ cells (Dulken *et al.*, 2017), suggesting that neurospheres in culture may depend on inflammation-associated molecules for proper growth. In line with this notion, adult SVZ cells (microglia and neural stem/progenitors) in culture released IL-1β, IL-4, IL-6, IL-10, and GM-CSF, whereas only IL-1β and GM-CSF were released by cortical cells (Ribeiro Xavier *et al.*, 2015a) and similar results were found in postnatal SVZ microglia (Shigemoto-Mogami *et al.*, 2014). IL-4 and IL-10 are anti-inflammatory and act via phosphorylation of STAT6. In contrast to cortical microglia, SVZ microglia expressed nuclear pSTAT6 suggesting an alternative state of activation (Ribeiro Xavier *et al.*, 2015a). Thus, despite these interesting data, the field needs a more comprehensive understanding of how SVZ inflammation is regulated at the molecular level and on the feedback of inflammation onto SVZ cells. A few relevant examples are provided below and we argue that these concepts may prove useful in the therapautic prevention or management of SVZ cancer.

2.3.1. Galectin-3 expression and function in the SVZ

The studies described above show that SVZ microglia are unusual and that they secrete inflammation-regulating molecules in a pattern different from the rest of the CNS. Possibly however, it is not the microglia but SVZ NSCs and progenitors that play a major role in controlling inflammation in the niche. One example that supports this possibility is the inflammation-regulating protein Galectin-3 (Gal-3) which is expressed by NSCs, progenitors and ependymal cells in the SVZ but not by microglial cells (Comte *et al.*, 2011). Galectins are evolutionarily ancient recognizers of bacterial glycoproteins and regulate immune and cancer cell chemotaxis and apoptosis (Liu and Rabinovich, 2005). They are upregulated in animals and humans after brain injury and disease, and Gal-3 is generally understood to have pro-inflammatory functions (Hillis *et al.*, 2016; James *et al.*, 2016; Young *et al.*, 2014a). Therefore it is important to note that during homeostasis Gal-3 is uniquely expressed in the SVZ at immunohistochemically detectable levels (Comte *et al.*, 2011). Gain and loss of function studies showed that Gal-3 is necessary for neuroblast migration from the SVZ to the OB (Comte *et al.*, 2011). Gal-3 function was shown to be important in the SVZ's response to TMEV, being necessary for immune cell infiltration into the SVZ, progenitor migration to demyelinated regions and SVZ proliferation (James *et al.*, 2016). Similarly, Gal-3 was also necessary for progenitor emigration induced by cuprizone from the SVZ into the demyelinated corpus callosum (Hillis *et al.*, 2016). Given these studies collectively show that Gal-3 regulates multiple aspects of SVZ progenitor migration in health and disease, it will be interesting to explore its role in SVZ cancer infiltration into surrounding tissues. Gal-3 is essential for macrphage immigration into inflammed obese tissues (Li *et al.*, 2016) and similarly is predicted to regulate macrophage infltration into SVZ cancers. A Gal-3 inhibitor (TD139) was well tolerated in Phase Ib/IIa clinical trials for idiopathic pulmonary fibrosis (Galecto Biotech) and should be tested in the context of SVZ-originating brain cancers.

2.3.2. Polarity, the Hippo pathways and ASPP2 in inflammation and cancer

Apicobasal cell polarity is a defining feature of SVZ NSCs which have an apical primary cilium extending between ependymal cells and in contact with CSF (Danilov *et al.*, 2009; Mirzadeh *et al.*, 2008). This primary cilium is the location of sonic hedgehog (SHH) signaling and thereby regulates NSC activation in the ventral SVZ (Ahn and Joyner, 2005; Ihrie *et al.*, 2011; Palma *et al.*, 2005). The basal pole of the astrocyte-like SVZ NSCs in turn extend laterally to contact blood vessels (Mirzadeh *et al.*, 2008). The basal processes regulate blood vessel diameter (Lacar *et al.*, 2012), similar to astrocytic processes in the rest of the brain which regulate neurovascular coupling (Attwell *et al.*, 2010; MacVicar and Newman, 2015). How inflammation affects this essential apicobasal cell polarity leading to SVZ tumorigenesis is poorly understood. Loss of apicobasal polarity is a central feature in epithelial mensenchymal transitions and escape of cancer cells from the primary tumor (Martin-Belmonte and Perez-Moreno, 2011; Moreno-Bueno *et al.*, 2008; Royer and Lu, 2011). Thus we predict that loss of apicobasal polarity is a prerequisite for NSC transformation into tumorigenic CSCs.

The Hippo tumor suppressor pathway is important for normal tissue growth and homeostasis and is a key signalling pathway that maintains cell polarity (Harvey and Tapon, 2007). Inflammatory stimuli regulate Hippo pathway activity during regeneration (Wang *et al.*, 2017b) but when polarity is lost this same process can lead to cancer. Interestingly, the Hippo pathway regulates primary cilia as well as cell division and differentiation in the brain (Huang *et al.*, 2016; Orr *et al.*, 2011). The main Hippo effector is the transcriptional coactivator Yes Associated Protein (YAP) which can interact with SHH

and promote growth of glioblastoma cell lines (Orr *et al.*, 2011). AP activity in turn can be inhibited by the tumor suppressor neurofibromatosis 2 (NF2) in neural progenitor cells (Lavado *et al.*, 2013; Orr *et al.*, 2011).

The Hippo pathway's role in inflammation can also be due to the control of tissue restoration. In a model of colitis, YAP does not affect normal tissue but it is necessary for healing, and this process can generate polyps and tumors when not balanced (Cai *et al.*, 2010; Kim *et al.*, 2017). Moreover, the loss of the Hippo upstream activator Ras association domain family member 1A (RASSF1A) has been widely linked to tumor onset and is a specific prognostic factor in all brain cancers, especially GBM (Grawenda and O'Neill, 2015). It was proposed that in early inflammation, loss of RASSF1A causes binding of YAP to p73 promoting transcription of genes involved with apoptosis. In contrast, prolonged colitis promotes the binding of YAP to TEAD, which results in tumorigenesis (Gordon *et al.*, 2013). A number of upstream inputs regulate the Hippo pathway and YAP in planar and apicobasal polarity including the Crbs complex, Fat cadherin, GPCR signalling, NF2, RASSF1, Sav1 and more recently the ASPP family via interaction with YAP1.

ASPP2 (apoptosis-stimulating of p53 protein 2) activates p53 and is a haploinsufficient tumor suppressor expressed in NSC, ependymal and choroid plexus cells (Sottocornola *et al.*, 2010; Turnquist *et al.*, 2014). Lipopolysaccharide (LPS) activates ASPP2 in microglia, macrophages and astrocytes in a STAT1-dependent manner (Turnquist *et al.*, 2014). In a maternal inflammation model, LPS induced ASSP2 expression in the choroid plexus (Turnquist *et al.*, 2014). Since ASPP2 is a tumor suppressor (Li *et al.*, 2015), it is a good candidate for controlling cancer development in the SVZ. Human tissue in neurodegenerative disease exhibits enhanced ASPP2 expression, whereas loss of ASPP2 results in enhanced inflammation, pointing to a model wherein ASPP2 is a "gatekeeper" of inflammation (Turnquist *et al.*, 2014). ASPP2 also regulates NSC cell polarity which when disrupted leads to cancer like neuroblastic rosettes (Sottocornola *et al.*, 2010) and we hypothesize that ASPP2 maintains the apicobasal polarity in SVZ NSCs and that loss of this polarity predisposes them to become tumorigenic.

3. Cancer Stem Cells Spring from the Subventricular Zone Stem Cell Niche

3.1. Brain cancers arising from the SVZ: clinical gliomas and ependymomas

Localization, stem cell markers and molecular alterations indicate that a subset of gliomas emerge from stem or progenitor cells in the SVZ. Magnetic resonance imaging demonstrate that human gliomas can physically associate with the SVZ and this is strongly correlated with a poorer prognosis based on several criteria including survival rate, volume, recurrence pattern, invasiveness and progression (Bohman *et al.*, 2010; Chen *et al.*, 2015; Jafri *et al.*, 2013; Kappadakunnel *et al.*, 2010; Lim *et al.*, 2007; Liu *et al.*, 2016; Liu *et al.*, 2017; Mistry *et al.*, 2017b; Vergani *et al.*, 2011; Young *et al.*, 2011b). Glioblastomas in contact with the SVZ can migrate/infiltrate not just in the RMS but in multiple directions, a pattern followed by endogenous SVZ cells during embryonic and postnatal development (Adeberg *et al.*, 2014b; Chen *et al.*, 2015; Gupta *et al.*, 2014; Lim *et al.*, 2007). This could explain why periventricular tumors are more likely to be multifocal and present relapses that are not contiguous with the primary site. Finally, tumors in the

SVZ have a stem-like profile and are associated with specific genetic alterations that support cell growth, proliferation and survival via altered metabolic programs, centromere assembly, chromosome segregation, epigenetic modifiers and increased ribosomal biogenesis (Haskins *et al.*, 2013; Jungk *et al.*, 2016; Lin *et al.*, 2017).

Stem and neural progenitor cell markers expressed in the SVZ are also found in gliomas physically associated with the SVZ, including glioblastomas (Bradshaw *et al.*, 2016). Periventricular astrocytomas of various grades express GFAP, nestin and vimentin and this expression correlates with invasiveness, possibly through increased levels of Annexin A2 (Brehar *et al.*, 2015; Haskins *et al.*, 2013). A proteomics analysis showed high expression levels of DCX, GFAP and vimentin in glioblastomas contacting the SVZ (Haskins *et al.*, 2013). Besides, DCX+ cells were strongly correlated with c-Myc expression in those tumors and in the SVZ, suggesting a subpopulation of cells with possible growth advantage (Haskins *et al.*, 2013). Olig2+ cells were found in proneural glioblastomas (Verhaak *et al.*, 2010) and studies on animal models of gliomagenesis suggested Olig2+ cells in the SVZ as a potential origin of gliomas (Wang *et al.*, 2009), including the proneural subtype (Lu *et al.*, 2016). Interestingly, proneural and neural glioblastomas were closer to the SVZ than the other subtypes (Steed *et al.*, 2016). Subependymomas may arise from multipotent cells in the SVZ and express glial and stem cell markers such as GFAP, Olig2 and Sox2 (D'Amico *et al.*, 2017).

The SVZ stem cell niche can be tumorigenic in likely due at least in part to stem cells maintaining intrinsically active signalling pathways that are altered in tumors, making them susceptible to malignancy upon further stimuli. In the SVZ, pathways such as the EGFr promote proliferation and are altered in several gliomas due to the amplification of its receptor, contributing to malignant transformation (Sanai *et al.*, 2005). The SHH pathway is vital in controlling stemness in the SVZ (Daynac *et al.*, 2016) and can be altered and trigger tumors through canonical and non-canonical mechanisms (Alvarez-Buylla and Ihrie, 2014; Clement *et al.*, 2007; Sanai *et al.*, 2005).

3.2. The SVZ is a "growth factory"

The specialized SVZ niche derives its unique identity and functions in large part due to the molecular environment it self-creates. Several neurotrophic growth factors are produced by NSCs and TAPs in the SVZ stem cell niche. Other cells present in this niche, such as ependymal cells, niche astrocytes, blood vessel endothelial cells, pericytes and microglia can also contribute to produce growth factors. These molecules function on NSC and TAPs in both autocrine and paracrine fashion and exert pleiotropic and redundant functions, regulating multiple cellular processes, such as growth, differentiation, survival and migration. The growth factors include brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), fibroblast growth factor-2 (FGF-2), vascular endothelial factor (VEGF), insulin-like growth factor-1 (IGF-I), hepatocyte growth factor (HGF), and nerve growth factor (NGF) among others (Yu *et al.*, 2016). Platelet-derived growth factor (PDGF), secreted by astrocytes and neurons, is a potent mitogen for oligodendrocyte progenitors (Noble *et al.*, 1988; Raff *et al.*, 1988; Richardson *et al.*, 1988). Besides these molecules, cytokines produced in other sites of the body are able to cross the blood-brain barrier and induce proliferation and differentiation of NSC and TAPs in the SVZ; these include erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF) (Yu *et al.*, 2016).

These growth factors and cytokines signal through receptor tyrosine kinases and in cancer their aberrant activation affects proliferation, survival and metastasis (Lemmon and Schlessinger, 2010; Regad, 2015). Moreover, human gliomas themselves produce some of these growth factors (ex., PDGF-A, -B, -C, -D, bFGF) (Hermanson *et al.*, 1992; Hermansson *et al.*, 1988; Lokker *et al.*, 2002; Takahashi *et al.*, 1990; van der Valk *et al.*, 1997) and their cognate receptors (EGFR, PDGFR) (De Bustos *et al.*, 2005; Hermanson *et al.*, 1996; Hermanson *et al.*, 1992; Hermansson *et al.*, 1988; Toepoel *et al.*, 2008; Torp *et al.*, 1991; van der Valk *et al.*, 1997) suggesting that paracrine/autocrine signaling could play an important role in proliferation and motility of SVZ cancer cells. Activation of the EGF and PDGF-pathways by gene amplification and/or overexpression are striking features of gliomas (Fleming *et al.*, 1992), and EGFR amplification has been observed in 35-70% of glioblastomas (Ohgaki and Kleihues, 2007; Okada *et al.*, 2003; Sauter *et al.*, 1996), while PDGF and/or PDGFR amplification occurs in 13% of glioblastomas, >80% of oligodendrogliomas and in 50-100% of astrocytomas (Guha *et al.*, 1995; Varela *et al.*, 2004). In pathogenic conditions, expression of the plethora of growth factors mentioned above can be dysregulated creating favorable circumstances for the initial expansion and selection of genetically mutated clones arising from SVZ stem or progenitor cells leading to cancer.

3.3. SVZ stem cells as a potential source of brain cancer

3.3.1. SVZ cells can be "pushed" to a stem cell phenotype

A central axiom in biology is that development is unidirectional. Totipotent stem cells give rise to pluripotent and then multipotent cells which give rise to lineage committed progenitors that generate post-mitotic differentiated cells. Dedifferentiation and acquisition of developmentally less mature stem cell characteristics does not occur spontaneously. This has been challenged by artificially inducing developmental reversal via somatic cell nuclear transfer (SCNT) and induced pluripotent stem cell (iPSC) approaches. Both laboratory techniques show that adult cells or nuclei can be induced to acquire early stem cell characteristics via exposure to embryonic cytoplasm or transcription factors. Brain cells can acquire iPSC characteristics via Oct4 expression alone, one of the four "Yamanaka" transcription factors required for reprogramming (Kim *et al.*, 2009a; Kim *et al.*, 2009b). In these experiments only a small percent of cells could be reprogrammed with Oct4 suggesting they may have been cells with immature characteristics such as SVZ cells. The development of SCNT and iPSC technologies spurred investigators to push the limits of unidirectional lineage progression with other approaches such as direct conversion. Direct phenotypic conversion bypasses intermediate mitotic events and induces phenotypic shifts (Arlotta and Berninger, 2014) within the same cell, showing that adult cells are indeed plastic and can acquire not only embryonic but alternative adult phenotypes. Other work has shown that outside the neurogenic niches astrocytes can be induced by injury and/or molecular regulation to re-enter the cell cycle and to become neurogenic (Buffo *et al.*, 2008). These remarkable studies beg the question to what extent do cancer cells in the SVZ exhibit mutation or environment-induced "reprogramming" or "direct conversion"?

It is conceptually easier for less committed or undifferentiated cells to turn backwards and acquire stem cell characteristics (Zhou and Melton, 2008). In fact early work suggested that SVZ TAPs can acquire stem cell-like characteristics when exposed *in*

vivo to EGF (Doetsch *et al.*, 2002). EGF exposure via Alzet mini-pumps in these experiments reduced expression of the proneurogenic transcription factor Dlx2 in transit amplifying progenitors. This is an important finding because more stem cells means there are more cells that could acquire a tumorigenic CSC phenotype. It is unclear however if endogenous levels of EGF can be sustained at high enough levels to induce acquisition of stem cell characteristics by SVZ cells, although this may occur in chronic disease. EGF signaling may also reverse the behaviour of doublecortin (Dcx+) neuroblasts. A subset of Dcx+ cells express the epidermal growth factor receptor (EGFr) and when these receptors were stimulated there was a 40% decrease in the number of migrating neuroblasts (Kim *et al.*, 2009c). Reprogramming of SVZ NSCs has also been achieved via administration of Oct4, which resulted in them generating midbrain dopaminergic neurons (Deleidi *et al.*, 2011). Although SVZ cells can generate dopaminergic progenitors (Betarbet *et al.*, 1996) that become interneurons in the olfactory bulb, these are quite different in ontogeny and function from the dopaminergic neurons generated by Deleidi and colleagues, whose experiments thus show acquisition of a more primordial NSC capacity. Ependymal cells are generally thought to be post-mitotic yet after models of stroke they also can re-enter the cell cycle and acquire a stem cell-like phenotype (Carlen *et al.*, 2009; Young *et al.*, 2013).

The reversal of developmental trajectory described above is reminiscent of cancer stem cells that arise from adult somatic cells. Theoretically any of the myriad cell types in the SVZ could acquire mutations and become tumorigenic and a variety of cells in the murine SVZ can become cancerous (Jackson *et al.*, 2006). Regardless of which cell is the origin of any given SVZ cancer, we predict that dedifferentiation will usually accompany the process. The type of cell that becomes tumorigenic likely will influence the relative malignancy and the behaviour of the cells and this may partly explain glioblastoma heterogeneity. We hypothesize that SVZ NSC, when rendered tumorigenic would give rise to cancers with profound and long-lasting self-renewal and broad fate potential. Transformation of TAPs, in turn would result in highly proliferative tumors whereas transformation of neuroblasts would result in highly infiltrative lesions. These predictions can be tested by selectively introducing mutations into specific SVZ cell types. Thus we favour a model wherein the ultimate nature of the tumor is influenced by the origin of the CSC.

3.3.2. SVZ cancers modeled in mice

Animal models, including knock-in mutations, growth factor infusions and human-rodent xenografts have created a variety of cancerous growths and revealed several molecular mechanisms resulting in tumorigenesis in the SVZ (Table 1) (Abel *et al.*, 2009; Breunig *et al.*, 2016; Feliciano *et al.*, 2012; Zhou *et al.*, 2011). The evidence for SVZ involvement in gliomagenesis gained traction with a series of *in vivo* experiments showing that malignant transformation preferentially occurs in proliferative areas of the brain (Sanai *et al.*, 2005). Mouse models have been created showing that gliomas can be induced by forced expression of PDGF in the brain (Nazarenko *et al.*, 2012). Excessive PDGFr activation in the SVZ of adult mouse brain, by exogenous administration of PDGF, induced the proliferation of PDGR-α-positive NSCs contributing to the generation of glioma-like lesions (Jackson *et al.*, 2006). Similarly, adult white matter glial progenitors, expressing PDGF-B by retroviral transduction, cause the transformation of oligodendrocyte progenitor cells (OPC) and development of glioblastomas (Assanah *et al.*, 2006).

Animal models using Cre-loxP or replication competent avian-like sarcoma (RCAS) virus / tumor virus receptor-A (tv-a) approaches show that mutations commonly found in gliomas create pre-lesions that evolve into gliomas when selectively induced in cells expressing stem cell promoters such as GFAP or Nestin. Using the Cre-loxP system Tp53 null mice were further altered by conditional loss of Pten and/or Nf1 under the control of the GFAP promoter resulting in stem cell-like gliomas (Kwon *et al.*, 2008; Zhu *et al.*, 2005). The same alterations driven by the nestin promoter (tamoxifen-inducible Cre-ERT) generated high grade astrocytomas even when induced in adult animals (Alcantara Llaguno *et al.*, 2009). Targeting the overexpression of Akt1 and Kras to GFAP and Nestin+ cells in the SVZ produced high grade gliomas (Abel *et al.*, 2009; Holland *et al.*, 2000; Marumoto *et al.*, 2009). Significantly, the same alterations in differentiated cells in other brain regions did not induce tumorigenesis (Abel *et al.*, 2009; Alcantara Llaguno *et al.*, 2009; Holland *et al.*, 2000; Marumoto *et al.*, 2009). Tp53 depletion and overexpression of PDGFA in the SVZ using RCAS/tv-a under the control of GFAP or nestin promoters generated tumors (Hambardzumyan *et al.*, 2011) with proneural glioblastoma subtype characteristics (Connolly *et al.*, 2017). Overexpression of PDGF in other areas of the brain was also able to produce tumors, suggesting it can act in different subpopulations of cells to give rise to gliomas (Connolly *et al.*, 2017; Hambardzumyan *et al.*, 2011).

Another widely used model of glioma is treatment with the mutagen N-ethyl-N-nitrosourea (ENU), resulting in SVZ tumors with stem cell marker expression (Garcia-Blanco *et al.*, 2016; Mennel and Simon, 1985). Cells became prone to generate tumors in the SVZ after Tp53 tumor suppressor loss, but additional stimuli such as ENU were necessary for full gliomagenesis (Gil-Perotin *et al.*, 2006). The ENU carcinogen alterations included increased proliferation and angiogenesis through the activation of the AKT and ERK pathways (Bhaskara *et al.*, 2006), β-catenin (Sareddy *et al.*, 2009) and VEGF pathways (Bulnes and Lafuente, 2007). A subpopulation of cells isolated from the SVZ of mice transplacentally exposed to ENU became immortalized and it was found that they harbored homozygous deletion of INK4a/ARF (Savarese *et al.*, 2005). Homozygous deletion of INK4a/ARF is a common event in classical glioblastomas and is highly associated with EGFR amplification (Verhaak *et al.*, 2010). SVZ NSCs with deletion of Ink4a/Arf and constitutively active EGFR when orthotopically transplanted into mice generated tumors that expressed progenitor markers (Bachoo *et al.*, 2002). In addition, the RCAS/tv-a system was used to show that the deletion of Ink4a/Arf in combination with activation of Kras and Akt in nestin-positive cells was able to generate glioblastomas (Uhrbom *et al.*, 2002). Cells respond to the tumorigenic stimuli caused by Akt and H-Ras by increasing levels of Sox 5/6/2, and the deletion of those proteins in the SVZ increases the potential of Akt and H-Ras to drive gliomagenesis (Kurtsdotter *et al.*, 2017). Together, these studies have revealed several inter-related mechanistic avenues and multiple SVZ cell sources for cancer generation. What is acutely missing is a comprehensive analysis of how inflammation is affected by these mouse models and if regulation of inflammation could influence their development.

3.3.3. IDH1 mutation as a model of cancer and inflammation in the SVZ

More than 70% of brain tumors are gliomas, with glioblastoma multiforme (GBM) being most frequent and malignant. Mutations in the active site of isocitrate dehydrogenase (IDH1/2) have been identified in 80% of low grade gliomas and secondary GBMs, and persist in recurrent lesions (Dang *et al.*, 2016). Thus IDH has been identified as a main driver gene in this disease, and its mutations are believed to be an early event

in gliomagenesis. How IDH1 mutations contribute to tumorigenesis is mostly unknown. This enzyme converts isocitrate to α-ketoglutarate (αKG), but when mutated, IDH1 possess a novel enzymatic function that reduces αKG to 2-hydroxyglutarate (2HG). 2HG is thought to act as an oncometabolite, by inhibiting αKG-dependent enzymes. These include enzymes involved in DNA and histone demethylation among others (Dang *et al.*, 2016). IDH1/2 mutant gliomas are characterized by genome-wide epigenetic changes, such as GpC island methylation (CIMP) and are associated with a better prognosis compared to patients with wild type IDH tumors. Recently Amankulor et al. showed that IDH1 mutations cause a reduction in leukocyte infiltration into gliomas, leading to a suppression of the tumor associated immune system. The authors suggest that this inhibited immune response contributes in part to the difference of aggressiveness of IDH-mutant tumors compared to their wild counterparts (Amankulor *et al.*, 2017). Other studies showed that expression of mutant IDH or a treatment with 2HG reduced infiltration of cytotoxic CD8+ T lymphocytes within the tumor and levels of T cells-associated effector molecules and chemokines, such as CXCL10. Notably these effects were reversible by using IDH-C35, a specific inhibitor of mutant IDH1(Kohanbash *et al.*, 2017). Along the same line, glioma cells and astrocytes expressing IDH-mutations are able to escape natural killer cell-mediated cytotoxicity, by decreasing NKG2D ligand expression and IFN-γ secretion (Zhang *et al.*, 2016). Consequently, these data suggest that mutant IDH is able to decrease the levels of immune surveillance, enabling tumor cells to escape it; this might allow tumor growth and progression. Recently, mice expressing mutant Idh1 in the SVZ were shown to develop features of gliomagenesis (Fig. 1) (Bardella *et al.*, 2016). Mutant SVZ cells increased proliferation both in TAPs and in NSC, infiltrated into surrounding regions and expressed genes associated with proneural glioblastoma and Wnt signaling (Bardella *et al.*, 2016). Given the SVZ stem cell niche has an atypical inflammatory response, it will be important to investigate the function of mutant-IDH on immune and inflammatory cells in this specific microenvironment, especially to evaluate a possible role during tumor initiation.

3.4 SVZ cells can modulate cancer stem cells

The SVZ can generate tumors, but it is also important to consider how SVZ cells that are not transformed can modulate CSC and gliomagenesis. SVZ progenitors migrated towards striatal glioma in vivo and surrounded it and similarly SVZ cells in explants in vitro migrated towards glioma cells (Glass *et al.*, 2005; Walzlein *et al.*, 2008). This tropism decreased with age and was associated with increased cancer progression and decreased survival rates (Glass *et al.*, 2005; Walzlein *et al.*, 2008). Co-culture experiments also showed that SVZ cells limited tumor growth and increasd apoptosis of cancer cells (Glass *et al.*, 2005). Thus SVZ cells that emigrate to cancer may be beneficial.

Conversely, other evidence suggests that glioma cells migrate into the SVZ and become more dangerous. Human glioma cells injected into the striatium homed to the SVZ and then migrated to the OB via the RMS (Kroonen *et al.*, 2011). The cancer cells that migrated into the SVZ had a strong tumorigenic capacity upon secondary transplantation (Kroonen *et al.*, 2011) and had enhanced migratory responses to chemokine signalling in vitro (Goffart *et al.*, 2015). SVZ cell-conditioned medium stimulated in vitro glioblastoma migration in a CXCL12/CXCR4 chemokine-dependent manner (Goffart *et al.*, 2015). This signalling pathway may be a good target for adjunct therapy since glioblastoma cells that have migrated into the SVZ are resistant to radiotherapy (Goffart *et al.*, 2017). Recently, a

pathogenic interaction between TAPs and glioma cells was demonstrated: TAPs produced chemoattractants toward which glioma cells homed. Amongst these SVZ TAP-secreted factors, the neurite outgrowth-promoting factor pleiotrophin along with its binding partners SPARC/SPARCL1 and HSP90B were the main mediators of this interaction (Qin *et al.*, 2017). Once arrived to the SVZ stem cell niche, glioma cells can then be encouraged to grow and form colonies by growth factors present in this specific microenvironment. Overall, these data are commensurate with the notion that the SVZ produces a variety of proteins including chemokines and growth factors that provide a chemoattractant and regulatory environment for cancer cells.

4. Interactions between Subventricular Zone Cancer Cells and Inflammation

4.1. Inflammation can predispose tissues to mutations and cancer

Inflammation is driven by cells of the immune system and in physiological conditions is designed to fight infections and heal wounds. However, inflammation can also have tumor-promoting effects and has been widely recognized as one of the hallmarks of cancer (Hanahan and Weinberg, 2011). Inflammatory responses coordinate the cells in the tumor microenvironment, which include tumor cells, inflammatory cells, immune cells, endothelial cells, and extracellular matrix. Similar to the SVZ neurogenic niche, several cytokines, chemokines and growth factors are produced by cells in tumor microenvironments, resulting in complex cellular interactions and regulation of multiple cellular processes. In particular, inflammation produces molecules, such as growth factors that promote cell proliferation, survival factors that reduce cell death, pro-angiogenic factors and extracellular matrix proteases, that facilitate angiogenesis, invasion and migration, and signals activating epithelial to mesenchymal transition (Hanahan and Weinberg, 2011); altogether these responses can contribute to the onset and progression of cancer.

However, cancer-related inflammation may also contribute to mutagenic load of tumor cells, by causing accumulation of random genetic alterations. Inflammatory cells can release reactive oxygen species and reactive nitrogen intermediates that are capable of inducing DNA damage and genomic instability in nearby cancer cells, accelerating their genetic evolution toward malignancy (Grivennikov *et al.*, 2010). Inflammation may also cause genetic instability through another mechanism. By affecting the function or expression of mismatch repair genes or of their corresponding enzymes, it may disturb safeguarding of genomic integrity. These mechanisms include expression of HIF1α by inflammatory cytokines (TNF and IL-1β, downregulation of MutS protein homolog 2 and 6 (*MSH2* and *MSH6)* by reactive oxygen and nitrogen species, direct oxidative inactivation of mismatch repair enzymes by hydrogen peroxide, and downregulation of mismatch repair family member MutL homolog 1 (*MLH1*), by nitric oxide (Colotta *et al.*, 2009). Once the mismatch repair system has been inactivated, the rate of mutagenesis induced by inflammation can increase and genes harbouring microsatellites in their coding regions, included tumor suppressor genes can be inactivated (Colotta *et al.*, 2009). Moreover cancer-related inflammation can alter cell cycle checkpoints, possibly causing chromosomal instability. Nitric oxide and its derivatives inhibit the function of the mitotic checkpoint p53 and are also associated with p53 mutations (Colotta *et al.*, 2009). Growth factors and chemokines released by inflammatory cells in the tumor microenvironment can also increase expression of the transcription factor c-Myc. Expression of this oncogene

can increase the intrinsic mutation rate of cancer cells and impair genome integrity by different mechanisms, which include the induction of double strand breaks by the production of ROS (Colotta *et al.*, 2009). Thus we hypothesize that the low-grade constitutive inflammation of the SVZ may predispose SVZ cells to become tumorigenic through accumulated mutations and thereby begin a feed forward cycle of inflammation-driven cancer evolution. This hypothesis could be tested by determining the rate of somatic mutations in the SVZ compared to other brain regions.

4.2. Regulation of SVZ stem cells by inflammation

Inflammation triggered by the bacterial mimetic lipopolysaccharide (LPS), the viral mimetic polyinosinic-polycytidylic acid (polyI:C) or several cytokines was long-believed to be detrimental to neurognesis. Early studies showed that inflammation induced during adulthood diminishes SGZ neurogenesis which can be rescued by anti-inflammatory agents (Ekdahl *et al.*, 2003; Monje *et al.*, 2003). Maternal immune activation with LPS reduced ventricular proliferation in the developing cerebral cortex (Stolp *et al.*, 2011). Likewise, exposure to polyI:C during embryonic development decreased NSCs and neuroblast populations in the adult SVZ (Liu *et al.*, 2013). Persistent brain inflammation reduced the proliferation of NSCs and impaired neuroblast migration in the adult SVZ (Pluchino *et al.*, 2008) while the anti-inflammatory cytokine IL-10 kept NSCs proliferative and undifferentiated in the adult SVZ (Perez-Asensio *et al.*, 2013).

The one-sided view that inflammation simply reduces proliferation and neurogensis was challenged by studies suggesting that microglia and T cells can be beneficial for maintaining SGZ neurogenesis (Ziv *et al.*, 2006). Recent studies have shown that microglia can also have positive effects on SVZ neurogenesis. Activated microglia support enhance SVZ neurogenesis through cytokine release whereas microglial inhibition reduced cytokine secretion and decreased SVZ neurogenesis during early postnatal development (Shigemoto-Mogami *et al.*, 2014). Although microglial depletion increased proliferation in the adult SVZ, intact microglia were crucial for the survival and migration to the OB of adult SVZ neuroblasts (Ribeiro Xavier *et al.*, 2015b). In another "positive" study, the pro-inflammatory cytokine TNFα increased NSC proliferation in adult SVZ neurosphere culture (Widera *et al.*, 2006).

Taken together, inflammation can result in positive or negative effects on SVZ neural stem cells and neurogenesis. The data suggest that the effects of inflammation in the SVZ are difficult to predict. This binary effect of inflammation likely depends on a number of factors such as the type of inflammatory stimuli, cell types involved in the response and the time and context of the inflammatory insult. These factors may also influence whether microglia acquire an M1 phenotype (cytotoxic) or an M2 phenotpye (neuroprotective) resulting in differential effects on SVZ neural stem cells. Classically activated M1 microglia can induce astrocytes to become neurotoxic via Il-1α, TNF and C1q (Liddelow *et al.*, 2017). This form of astrocytic toxicity has been implicated in neurodegenerative disease and it will be important to determine if SVZ microglia stimulate SVZ NSC or niche astrocytes in a similar manner in the context of cancer. Whether cancer-induced inflammation has positive or negative effects on SVZ cell proliferation and indeed on SVZ CSC themselves should also be resolved in order to develop viable therapeutic options.

4.3. Drugs for inflammation and SVZ cancer

Multiple pharmacological approaches are becoming feasible for targeting SVZ CSC. A huge wealth of information has emerged on the molecular mechanisms regulating many aspects of SVZ neurogenesis. Given that these mechanisms are often co-opted by SVZ cancers, target discovery approaches seem viable. Alternatively, phenotypic screen-based drug discovery seeking to limit SVZ proliferation, increasing differentiation or increasing apoptosis, could be developed to tackle periventricular tumors (Moffat *et al.*, 2017). However, this has to be done carefully as hippocampal neurogenesis is important for memory and hypothalamic neurogenesis may be important for longevity (Zhang *et al.*, 2017). Drugs have in fact been found that promote neuronal differentiation (Wurdak *et al.*, 2010). One example that could be used to treat SVZ cancers is the small molecule KHS101, which inhibits proliferation of progenitor cells and favors neuronal differentiation by allowing the activity of the transcriptional factor ARNT2 (Wurdak *et al.*, 2010). Drugs are being developed to stimulate neurogenesis for neurodegenerative disease, although, those that increase survival (Pieper *et al.*, 2010) or activate stem cells would not be appropriate for cancer.

Instead of targeting neural CSC proliferation or invasion, drugs targeting inflammation should be considered. Several drugs which target inflammation are beneficial in multiple sclerosis (Dendrou *et al.*, 2015) and could be repurposed for cancer therapy. Epidemiologic studies have shown that anti-inflammatory use is protective against gliomas, for example regular use of non steroidal anti-inflammatories reduced glioma risk by 33% (Scheurer *et al.*, 2008; Sivak-Sears *et al.*, 2004). In gliomas,TGF-β can be secreted by cells including microglia and macrophages and, through abnormal signalling, can have either pro- or anti-tumorigenic actions particularly on CSC (Han *et al.*, 2015; Joseph *et al.*, 2013). Several approaches aiming to target TGF-β signaling in gliomas have been tested and acheived encouraging results (Han *et al.*, 2015; Joseph *et al.*, 2013). For example, the TGF-β-activated kinase-1 (TAK1) is known to regulate inflammation in diverse types of cancer and in multiple sclerosis (Sakurai, 2012). Conditional TAK1 depletion specifically in microglia reduces central nervous system inflammation and is helpful in multiple sclerosis (Goldmann *et al.*, 2013). As well, TAK1 inhibitors have proven effective in cancer therapy (Sakurai, 2012; Totzke *et al.*, 2017). Recently, the inhibitor Takinhib was found to have high specificity for both autophosphorylated and non-phosphorylated TAK1 and induced cell death in metastatic breast cancer cells (Totzke *et al.*, 2017).

Anti-inflammatory drugs are important candidates for treatment of gliomas due to their ability *in vitro* and *in vivo* to supress proliferation and migration and to promote apoptosis. Sulfasalazine, is effective in inflammatory bowel disease and targets human glioma CSC in a xenograft model by inhibiting the cystine–glutamate transporter (xCT) and promoting caspase-mediated apoptosis (Chung *et al.*, 2005). Sulfasalazine does not cross the blood-brain barrier, although it successfully increased survival of orthotopic transplanted xenografts when locally delivered (Haryu *et al.*, 2018). In another positive development, a range of plant-derived anti-inflammatory drugs are being proposed as treatments because of their anti-glioma activity and their capacity to cross the blood-brain barrier. Withaferin A, Dehydrocostus lactone and Evodiamine are examples of compounds which presented encouraging results via mechanisms involving inflammatory pathways (Dhami *et al.*, 2017; Hou *et al.*, 2017; Marlow *et al.*, 2017; Wang *et al.*, 2017a; Wu *et al.*, 2017). Finally, Gal-3 is known for its role in activating microglia and it can be overexpressed in gliomas (Liu and Rabinovich, 2005). As mentioned above, the Gal-3 inhibitor TD139 (Galecto Biotech) has been tested in idiopathic pulmonary fibrosis with

good results and it would be particularly interesting to analyze its effects in the context of periventricular gliomas.

Another way to approach inflammation in brain tumors is by specifically inhibiting glioma-associated macrophages and microglia (GAMs) which contribute to diverse aspects of tumorigenesis (Roesch *et al.*, 2018). In fact, several drugs that target microglia are already being tested in preclinical and clinical trials (Roesch *et al.*, 2018). Inhibition of GAM Mer tyrosine kinase receptor (MerTKr) by UNC2025 combined with fractionated external beam radiotherapy, increased mouse survival (Wu *et al.*, 2018). Finally, minocycline, a p38 MAP kinase inhibitor, supresses GAM activity and has been proposed as an adjuvant treatment for gliomas (Markovic *et al.*, 2011), however it must be approached with caution as it can also induce neuronal death and impair SVZ neuro and gliogenesis (Inta *et al.*, 2017).

Ependymal cells are a convenient target for gene therapy designed to influence SVZ gliomagenesis. Over a decade ago an adenoviral gene delivery strategy was developed in rats as proof-of-principle, with a secreted glycoprotein being selectively targeted to ependymal cells and expression sustained for an extended period of time (Bajocchi *et al.*, 1993). Since then ependyma-specific transcription factors such as FoxJ1 (Jacquet *et al.*, 2009) have been discovered and these can be co-opted via promoter specific driven constructs for selective ependymal cell targeting. Recent work in mouse has shown that ependymal viral targeting with the human lysosomal enzyme arylsulfatase A resulted in expression of up to one year (Yamazaki *et al.*, 2014). Ependymal cell targeting has also been used to treat a number of neurodegenerative diseases and offers the advantage of localizing increased gene expression to the interior of the brain, avoiding systemic effects (Sun *et al.*, 2017). Ependymomas themselves are conveniently located for gene therapy via the lateral ventricles. However in this case other promoter-based targeting strategies than FoxJ1 may have to be chosen given that FoxJ1 expression decreases in ependymomas (Abedalthagafi *et al.*, 2016). Mcidas and GemC1 are upstream of FoxJ1 and essential in ependymal cell differentiation (Kyrousi *et al.*, 2015) and may be good molecular targets for ependymoma gene therapy.

Discovery of the brain lymphatic system lends great hope for CNS drug delivery. Fortunately the SVZ lines the ventricular system which is an integral part of the brain's lymphatic drainage system (Engelhardt *et al.*, 2017; Sun *et al.*, 2017). The olfactory system is also known to be part of the brain lymphatic system with CSF egressing into the nasal cavity. However proteins can travel in the opposite direction from the nasal epithelium to the brain and several preclinical studies have shown therapeutic efficacy via this route (Fletcher *et al.*, 2009; Lin *et al.*, 2009; Scafidi *et al.*, 2014). Interestingly, intranasal delivery can also provide therapeutic benefit via modulation of inflammation (Cai *et al.*, 2011; Jiang *et al.*, 2011). Although controversial for many years, the nasal route of administration of drugs for CNS therapy is becoming well established and accepted (Sun et al, 2017). This route of administration may be exceptionally well-suited for targeting SVZ cancers.

Conclusions

A huge wealth of information about cell phenotypes and molecular mechanisms regulating neurogenesis in the SVZ has been generated in the last twenty years. This is advantageous in terms of helping the field understand how these cells and processes may

be transformed and become tumorigenic. Glioblastomas and other cancers can arise from the SVZ and can also be modeled in the niche in animals. The role of inflammation in this process is still poorly understood, but deserves in-depth study. This is likely to be complex as inflammation can have both positive and negative effects on SVZ proliferation. The regulation of SVZ inflammation in the context of pathology can differ dramatically compared to other brain regions. Once more in-depth information will be acquired on the specific roles of inflammation in different SVZ cancers, therapeutic interventions can be rationally considered. The SVZ is rather more accessible than other brain regions by virtue of its location next to the ventricles and thus the treatment of SVZ cancers may be more tractable than cancer found in other parts of the brain.

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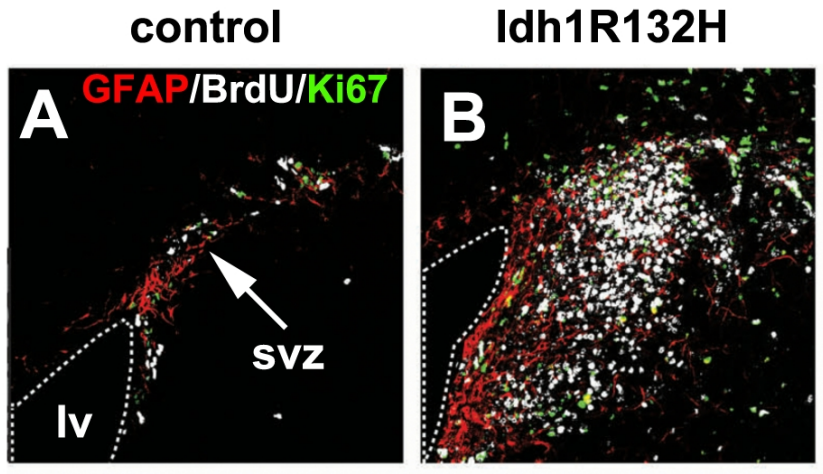
Figure Legends

Figure 1. The Idh1^{R132H} mutation knocked into the SVZ niche induces gliomagenesis. A) Control SVZ next to the lateral ventricle (lv) shows a typical distribution of GFAP+ (red), label-retaining BrdU+ cells (white) and acutely proliferating Ki67+ cells (green). B,C) These populations increased dramatically in the SVZ and striatum upon tamoxifen-induced conditional knockin of the Idh1^{R132H} mutation into nestin+ SVZ cells. D) Schematic of different cell types in the SVZ and their response to the IDH1 mutation. Note that it is not yet determined whether one type of TAP gives rise to lineage committed progenitors (as depicted) or if multiple distinct TAPs exist. Adapted from Bardella et al., 2016.

Figure 2. Glioma (Gl) associated with the human SVZ. The location of the contralateral SVZ is outlined in red and indicated with an arrow. Note that the glioma is pushing the lateral ventricle medially and the caudate nucleus (Cn) laterally. This glioma is likely heterogeneous and composed of many different types of cells as suggested by the multiple hues within it. From: https://library.med.utah.edu/WebPath/CNSHTML/CNS132.html

Figure 3. Schematic showing major points in the review about the relationships between cells and moelcules in homeostasis and cancer in the SVZ.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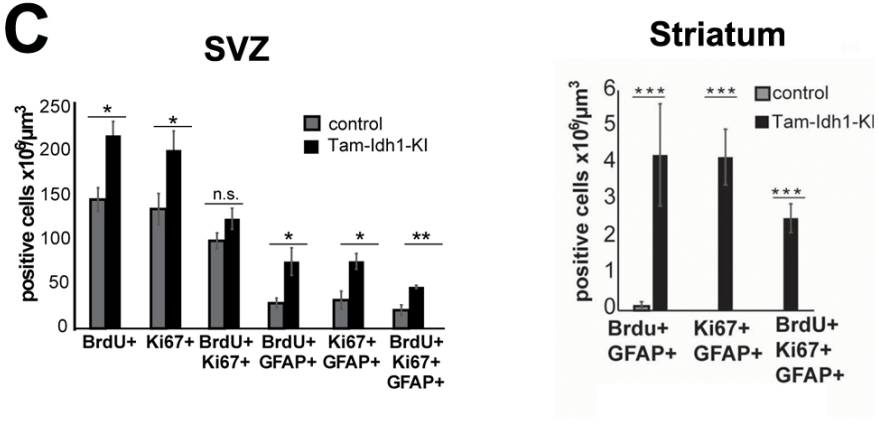
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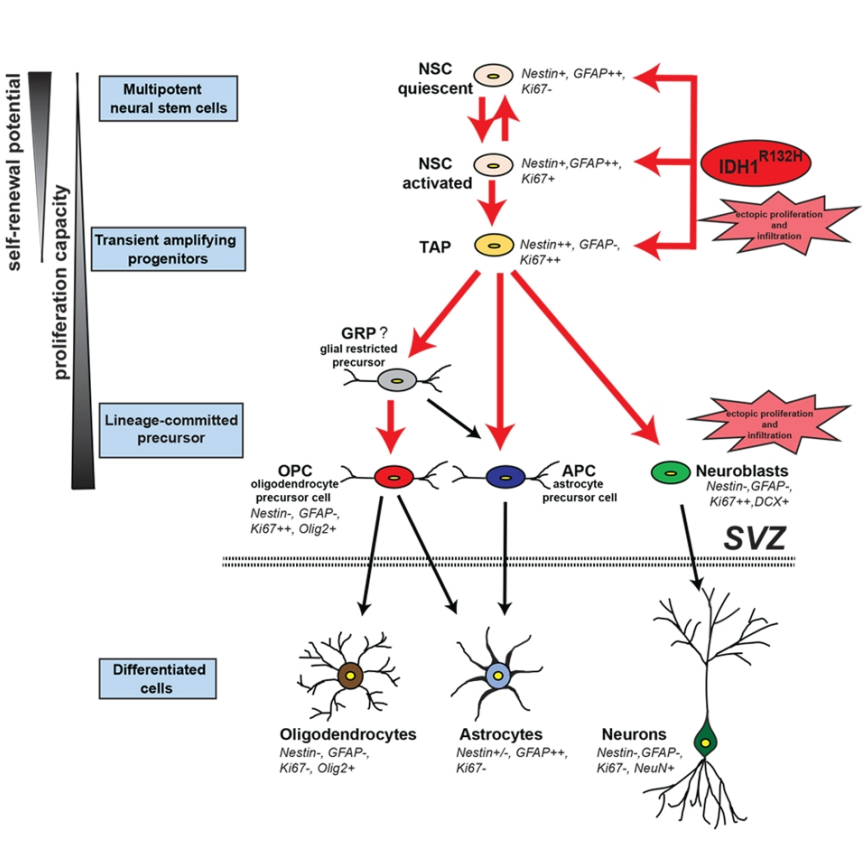
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self-renewal potential
proliferation capacity
Multipotent neural stem cells
Transient amplifying progenitors
Lineage-committed precursor
Differentiated cells
NSC quiescent
Nestin+, GFAP++, Ki67-
NSC activated
Nestin+,GFAP++, Ki67+
TAP
Nestin++, GFAP-, Ki67++
IDH1R132H
ectopic proliferation and infiltration
GRP ?
glial restricted precursor
OPC
oligodendrocyte precursor cell
Nestin-, GFAP-, Ki67++, Olig2+
APC
astrocyte precursor cell
Neuroblasts
Nestin-,GFAP-, Ki67++,DCX+
SVZ
Oligodendrocytes
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Neurons
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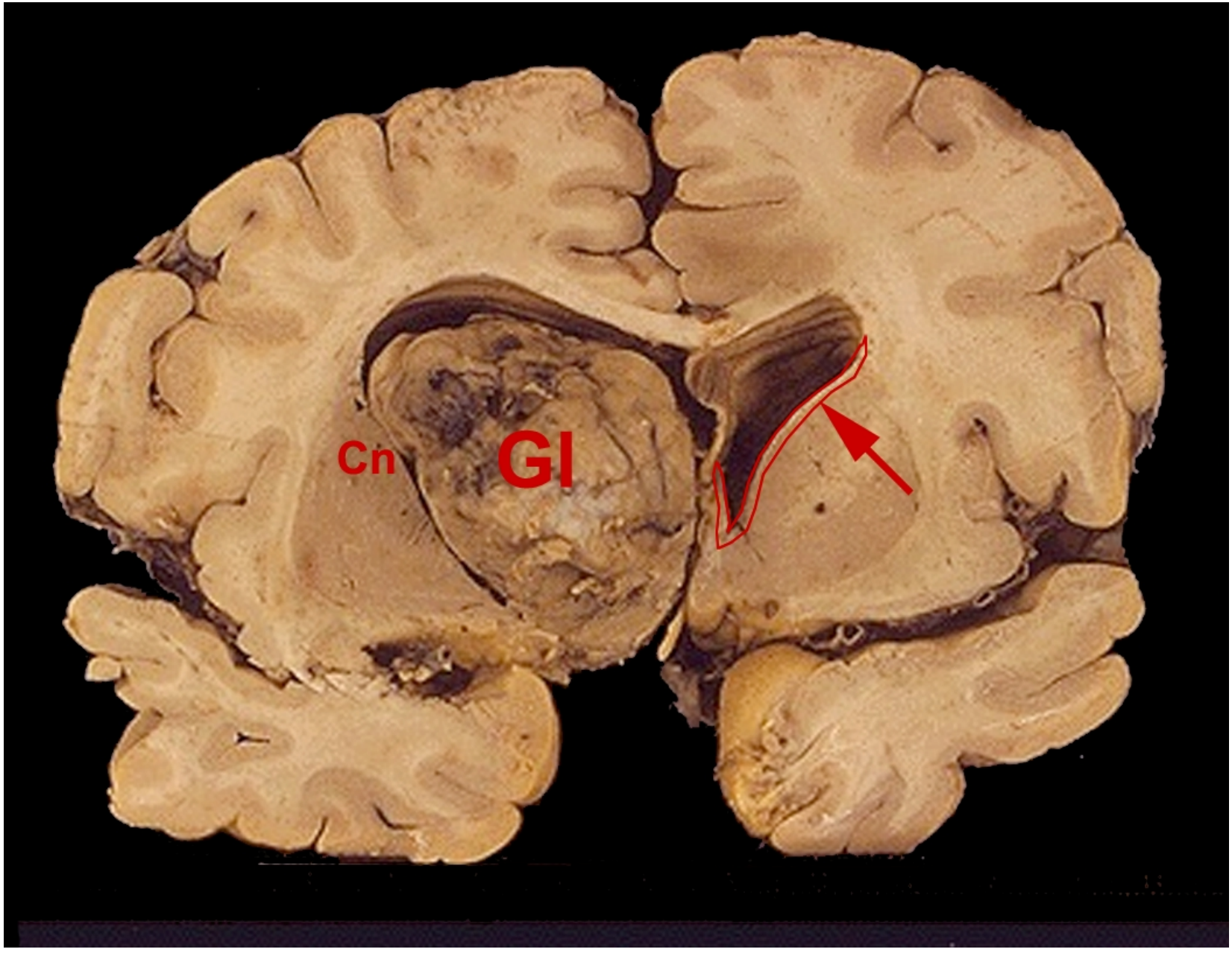
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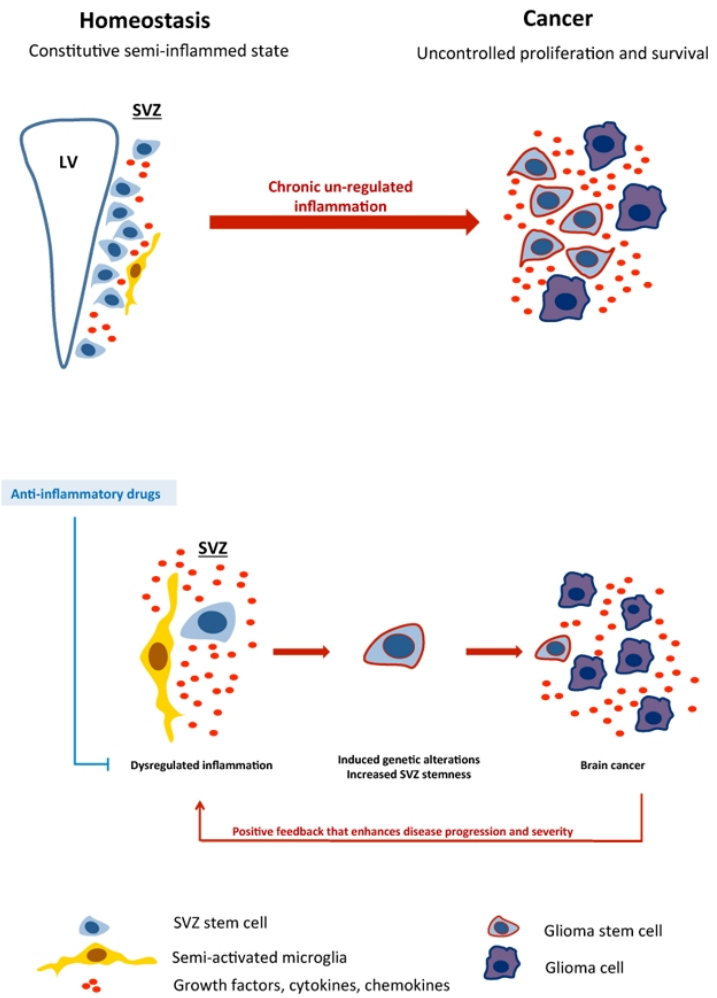

Proposed mechanistic links between SVZ inflammation, genetics and growth factor signaling in brain cancer formation.

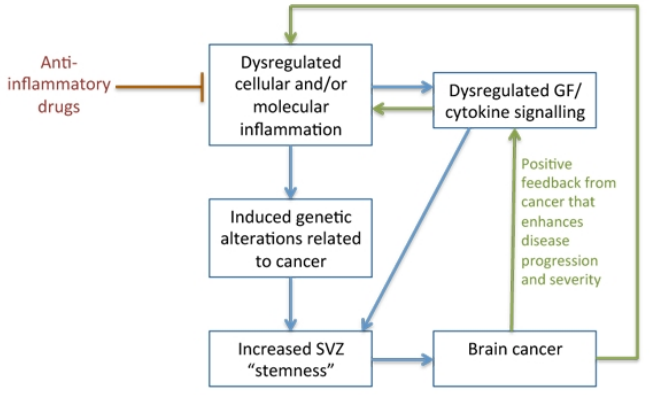

Table 1. Cancer models induced in rodent SVZ

Experimental approach, molecular mechanism	Main result	Implication, importance	Reference
$p53^{-/-}$ and $p53^{fl/fl}$ mice ± oncogenic ENU-induced mutations.	Loss of p53 function alone increases proliferation and differentiaton rate but is insufficient for transformation.	p53 + oncogenic mutations cause transformation of quiescent NSC.	(Gil-Perotin *et al.*, 2006)
PTEN loss of function induced by $PTEN^{+/-}$ introduced into a Nf1/p53 astrocytoma model in mice.	De novo high grade astrocytoma formation without intervening low-grade tumor.	Infiltration into various brain regions suggests an SVZ origin for the tumors.	(Kwon *et al.*, 2008)
Nestin-creERT2 mice bred with Nf1flox/+;p53flox/flox;Ptenflox/+ or Nf1flox/flox;p53flox/flox and adult mice treated with tamoxifen at 4 weeks of age.	Tumor suppressor inactivation in SVZ is both necessary and sufficient to induce astrocytoma formation.	All TMX mice developed astrocytomas. A pretumorigenic cell population *in vitro* showed growth advantage.	(Alcantara Llaguno *et al.*, 2009)
A p53 in-frame deletion mutation achieved by crossing GFAP-cre mice with p53 foxed mice.	Detectable mutant p53 first seen in SVZ NSC, progressing to Olig2+ transit amplifying progenitor like cells leading to astrocytma.	P53 loss by itself insufficient for tumorigenesis but allows subsequent mutations.	(Wang *et al.*, 2009)
Lentiviral induction of mutant H-Ras or Akt in GFAP+ cells ± $Tp53^{+/-}$ mutations using Cre-lox mice.	Massive tumours induced in SVZ or SGZ but not inthe cerebral cortex.	Convenient technique for introducing oncogenic mutations in specific cell type CRE driver lines.	(Marumoto *et al.*, 2009)
Activated Ras and Akt introduced into mouse SVZ or astrocytes.	Both molecules needed for transfrmation.	Induced high grade gliomas only via SVZ cells, not astrocytes.	(Holland *et al.*, 2000)
GFAP-Cre induced mutant K-ras.	SVZ increased proliferation and produced infiltrating gliomas.	This study suggests that tumor cells can derive from NSC, after being transformed by oncogenic $K\text{-}ras^{G12}$.	(Abel *et al.*, 2009)
SVZ electroporation in mice of mutant Ras and transposons for permanent integration.	Depleted NSC and upregulation of ETS factors.	Demonstrated that blocking ETS inhibits glioma formation.	(Breunig *et al.*, 2016)
$Sox5^{flox/flox}$ and $Sox6^{flox/flox}$ mice were injected with lentiviruses expressing CRE, HRas and AKT.	Loss of Sox5/6/21 dramatically increased glioma-like tumorigenesis.	Shows that Sox5/6/21 prevent HRAS and AKT induced oncogenic transformation.	(Kurtsdotter *et al.*, 2017)
Infusion of PDGF in mice activated the PDGFR.	Generation of glioma-like hyperplasias and blockade of neurogenesis.	One of the first papers to link fate choice with tumorigenesis.	(Jackson *et al.*, 2006)
Combination of mathematical modeling and RCAS/tv-a PDGF overexpression in murine GFAP+ SVZ cells.	Modeling predicts TAP cell of origin for symmetrical divisions induced by transformation otherwise a NSC origin.	PDGF OE in GFAP SVZ cells suggests modelling is correct.	(Hambardzumyan *et al.*, 2011)
Tsc1 loxP mice induced loss-of-function by crossing with Nestin-CreERT2 and Ascl1-CreERTM mice.	Appearance of subependymal nodules and subependymal giant cell astrocytomas. More severe phenotype in Nestin-Cre mice.	Phenotype hypothesized to be due to abnormal migration.	(Zhou *et al.*, 2011)
Tsc loss of function achieved with floxed mice crossed with Nestin-creERT2 or via Cre electroporation.	Migratory heterotopias and olfactory micronodules, migrating precursors infiltrated forebrain structures.	Suggest that emigration may contribute to psychiatric symptoms of tuberous sclerosis.	(Feliciano *et al.*, 2012)

Tamoxifen inducible knockin of $IDH1^{R132H}$ in Nestin-CreERT2+ mouse SVZ cells.	Increased self-renewal, proliferation, infiltration of all SVZ cell types - inducing a pregliomagenic phenotype.	First viable *in vivo* model of this common human GBM mutation. First mouse model showing that expression of $Idh1^{R132H}$ in mouse SVZ induces gliomagenesis.	(Bardella *et al.*, 2016)
In utero ENU exposure in rats caused homozygous deletion spanning the INK4a/ARF locus.	Induced transformation as indicated by blocked senescence.	Transformed SVZ cells model glioma precursors and can be a reservoir for further genetic/epigenetic hits leading to glioma.	(Savarese *et al.*, 2005)

ASPP2, apoptosis-stimulating protein of p53 with signature sequences of ankyrin repeat-, SH3 domain-, and proline-rich region-containing protein 2; **CD**, complement of differentiation; **CNS**, central nervous system; **CP**, choroid plexus; **CSC**, cancer stem cell; **CSF,** cerebrospinal fluid; **EGF**, epidermal growth factor; **EGFr**, epidermal growth factor receptor; **EPO**, erythropoeitin; **FGF2**, Fibroblast growth factor 2; **GBM,** glioblastoma multiforme, **GFAP**, glial fibrillary acidic protein; **G-CSF**, granulocyte colony-stimulating factor; **HGF,** hepatocyte growth factor; **IDH1**, isocitrate dehydrogeniase 1; **IFN-γ**, gamma interferon; **IGF-1**, insulin growth factor-1; **IL-10**, interleukin 10; **iPSC**, induced pluripotent stem cell; **NSC**, neural stem cell; **OCT4,** octamer-binding transcription factor 4; **PDGF**, platelet-derived growth factor; **PDGFr**, platelet-derived growth factor receptor; **RCAS**, replication competent avian-like sarcoma; **RMS**, rostral migratory stream; **ROS**, reactive oxygen species; **SCNT**, somatic cell nuclear transfer; **SDF-1**, stromal cell derived factor-1; **SHH**, sonic hedgehog; **SVZ,** subventricular zone; **TAP**, transit amplifying progenitor; **TMEV**, Thelier's murine encephalomyelitis virus; **TNFα**, tumor necrosis factor-alpha; **VEGF**, vascular endothelial growth factor.